Amendments to Specification

Please delete SEQ ID No. 1 and SEQ ID No. 2 from the sequence listing submitted February 14, 2003. Please replace the remaining sequence listing with the sequence listing filed electronically on November 20, 2003.

Please replace the paragraph in the abstract with the following:

A compound of formula (1), wherein: R_5 is hydrogen, C_{1-4}alkyl, R_6CH_2- or $R_6C(O)$-; R_6 is aryl, heteroaryl, heterocyclyl, aminoC_{3-6}alkyl, N-(C_{1-4}alkyl)aminoC_{3-6}alkyl, NN-(diC_{1-4}alkyl)aminoC_{3-6}alkyl, or R_7; wherein the aryl, heteroaryl or heterocyclyl rings may be optionally substituted with up to three substituents independently selected from nitro, C_{1-4}alkyl, C_{1-4}alkoxy, halo, (C_{1-4}alkyl)sulfanyl, C_{1-4}alkoxycarbonyl, N-(C_{1-4}alkyl)carbamoyl, NN-(diC_{1-4}alkyl)carbamoyl, N-(C_{1-4}alkyl)amino or NN-(diC_{1-4}alky)amino; wherein R7 is either a group or formula (2) or formula (3); and wherein L_1, L_2, L_3, L_4, R_1, R_2, R_3, R_4, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, A_1, n, p, q, r and s are as defined herein~~in claim 1~~. The compounds of formula (1) inhibit the interactions between MDM2 and p53 and may be useful in the treatment of cancers.

On page 1, please replace the paragraph at lines 4-8 with the following text:

This invention relates to compounds which inhibit the interaction between MDM2 ~~(SEQ ID NO: 2)~~ and the tumour suppressor protein, p53 ~~(SEQ ID NO: 1)~~. This invention also relates to processes for the manufacture of MDM2/p53 interaction inhibitors and pharmaceutically acceptable salts, prodrugs or solvates thereof, to novel pharmaceutical compositions containing them and to the use of the compounds as probes of MDM2 and p53 function.

On page 1, please replace the paragraph beginning at line 17 with the following:

MDM2 is a key negative regulator of p53 function, which binds to the amino terminal transactivation domain of p53. MDM2 both inhibits the ability of p53 to activate transcription and targets p53 for proteolytic degradation, thus maintaining the low levels of p53 under normal conditions. MDM2 may also have separate functions in addition to inhibition of p53. For example, MDM2 also binds another tumour suppressor protein, the retinoblastoma gene product, and inhibits ~~it~~ its ability to activate transcription. For

reviews of MDM2 function see: Piette et al (1997) Oncogene 15, 1001-1010; Lane and Hall (1997) TIBS 22, 372-374; Lozano and de Oca Luna (1998) Biochim Biophys Acta 1377, M55-M59.

On page 16, please replace the paragraph beginning on line 10 with the following:
The introduction of the $R_{5'}$ group when $R_{5'}$ is of the formula $R_6C(O)$- is carried out using standard methods know for the formation of an amide ~~bond. For~~ bond, as shown for example in the presence of HBTU as described above.

On page 25, please replace the paragraph beginning on line 19 with the following:
- The human MDM2 N-terminal fragment encompassing amino acids 1-118 and immediately followed by a C-terminal 6-histidine tag sequence and then a stop codon was generated by PCR from a human placental cDNA library. The PCR product was initially cloned into pCR2.1 vector (Invitrogen) following the ~~manufacturers~~ manufacturer's protocol. DNA sequencing confirmed a MDM fragment sequence identical to that ~~to~~ of published MDM2 (EMBL accession no. Z12020). The MDM2-6His fragment was then ~~suncloned~~ subcloned into pTB375 ~~E coli~~ E. coli expression vector to produce the expression vector pTB375-MDM2-6His (1-118) clone no. 11. The pTB375 vector is a modified T7 (Studier) Expression vector. Expression grows were performed in ~~E.coli~~ E. coli strain BL21 / DE3 (obtained from Novagen Inc.) and expression of the recombinant protein ~~protin~~ was induced by addition of IPTG (isopropyl-β-D-1-thiogalactopyranoside). MDM2 (1-118) 6 his was purified from ~~E.coli~~ E. coli lysates using Ni-NTA beads (Qiagen).

On page 26, please replace the paragraph beginning on line 9 with the following:
A DNA fragment encoding aa1-50 of p53 followed by a stop codon was generated by PCR using vector pHp53B (ATCC clone no. 57255) as template. The PCR product was initially cloned into pCR2.1 vector (Invitrogen) following the manufacturer's protocol. DNA sequencing confirmed a p53 sequence identical ~~to that to of~~ to that of published p53 (EMBL accession no. X04269).

On page 26, please replace the paragraph beginning on line 14 with the following:

The p53 fragment was then subcloned into pGEX-4T1 E coli expression vector (Pharmacia) to produce the expression vector pGEX-4T1-p53(1-50) clone no. 7.
The sequence of the expression vector at the junction of the GST and p53 sequences was as follows:

GST seq.....CTG GTT CCG CGT GGA TCC ATG..... (SEQ ID NO: 1)

(ATG is aa1 of p53, GGA TCC is the conserved BamHI cloning site)

Expression grows were performed in E. coli strain DH5alpha and expression of the recombinant protein was induced by addition of IPTG. GST-p53(1-50) was purified using glutathione-sepharose beads (Pharmacia). The procedures used for expressing the GST fusion protein are therefore analogous procedures to those disclosed by J. Han *et al.*, Journal of Biological Chemistry, 1996, 271, 2886-2891.